Overview of the Role of Inhaled Antifungals in Invasive Fungal Infections

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Outline

• Focus on pulmonary mold infections
• Infections: heterogeneity
• Risks and manifestations in specific patient populations
  – Hematologic malignancies
  – ICU (post-viral lung disease)
• Roles of inhaled antifungals
  – Prophylaxis, early prevention
  – Adjunctive therapy
Overview

- Disease is dependent on immunity with common early pathogenesis – poor clearance of inhaled conidia
- Goal of airway drug delivery dependent on host and stage: prevention and therapy
- Caveats
  - Use of different formulations, devices and treatment algorithms impairs conclusions from data presented to date
  - Overview of disease and clinical use: not drug specific
Mixed, multiple manifestations

Airways
Aspergillus overgrowth causes pathological airway inflammation and excess mucus production

Alveoli
Hyphal growth causes invasive pneumonia

Aspergillus

INVASIVE ASPERGILLOSIS TRACHEOBRONCHITIS POST-OBSTRUCTIVE BACTERIAL PNEUMONIA
Hematology / Oncology

- High risks for IMI with unique needs
  - Inhaled conidia ‘escape’ 1\textsuperscript{st} and 2\textsuperscript{nd} line defenses to invade into lung, +/- angioinvasion
  - Poor outcomes in treating advanced disease and difficult to diagnose
  - Azole-based prevention is a mainstay during periods of prolonged risks
    - Fluconazole, posaconazole
    - New therapies have presented unique unmet needs

Samanta and Nguyen. Fungal Gen & Patho 2017
Prevention POC shown for AmB in immunosuppressed animals

Trends in favor of prevention using inhaled AmB and L-AmB in different animal models

Xia et al. Ing J Infect Dis 2015
Inhaled AmB: 1990’s

**Table 1. Inhaled Amphotericin B for Prophylaxis of Invasive Aspergillosis in Hematology Patients**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Organism/Population</th>
<th>Prophylaxis</th>
<th>Antifungal</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz (1999)⁷</td>
<td>P, R, MC</td>
<td><em>Aspergillus</em> neutropenic leukemia, BMT, solid tumor MDS treatment (n = 227), control (n = 155)</td>
<td>IH AmBd started before onset of neutropenia and continued until 1 of 4 endpoints achieved</td>
<td>IH AmBd 10 mg bid</td>
<td>4% of treatment group vs 7% of control group developed IA (p = 0.37); 5% overall incidence</td>
</tr>
<tr>
<td>Conneally (1990)⁸</td>
<td>cohort</td>
<td><em>Aspergillus</em> neutropenic oncology, BMT, hematology treatment (n = 34), control (n = 123)</td>
<td>IH AmBd until ANC &gt;1/mL</td>
<td>IH AmBd 5 mg bid</td>
<td>0 of treatment group vs 14 of control group developed IA</td>
</tr>
<tr>
<td>Beyer (1993)⁹</td>
<td>P, case based</td>
<td><em>Aspergillus</em> germ cell tumors, BMT treatment (n = 40)</td>
<td>oral AmBd plus IH AmBd, mean length of inhaled therapy 17 days</td>
<td>oral AmBd 2400 mg qd plus IH AmBd 10 mg bid</td>
<td>incidence of IPA decreased with IH AmBd; 1 pt. had positive <em>Aspergillus</em> antigen on day 47, 1 pt. with documented IPA died from CNS toxicity and multi-organ failure, 1 pt. with pneumonia died 10 days post-BMT</td>
</tr>
<tr>
<td>Hertenstein (1994)¹⁰</td>
<td>observational</td>
<td><em>Aspergillus</em> neutropenia, BMT treatment (n = 303)</td>
<td>oral AmBd or fluconazole plus IH AmBd initiated 1–6 days before graft and continued until ANC &gt;1/mL</td>
<td>oral AmBd 500 mg qid (n = 283) or fluconazole 100 mg qd (n = 10) plus IH AmBd 10 mg bid</td>
<td>overall incidence of fungal infections 3.6% (n = 11), 8 infections due to <em>Aspergillus</em>, 8 pts. died despite IH AmBd and iv therapy, 4 infections occurred during neutropenia and IH AmBd</td>
</tr>
</tbody>
</table>
# Inhaled AmB prophylaxis

## Table 1. Clinical Trials for Prophylactic Nebulized Amphotericin B.

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>PATIENTS</th>
<th>DEMOGRAPHICS</th>
<th>STUDY POPULATION</th>
<th>DOSAGE</th>
<th>DISCONTINUATION CRITERIA/DURATION</th>
<th>OUTCOME</th>
<th>SIDE EFFECTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connelly et al[1]</td>
<td>InAmB D n = 34, historical control n = 123</td>
<td>NR</td>
<td>BMT recipients and acute leukemia</td>
<td>20 mg/4 mL over 10 min bid vs no inhalation</td>
<td>Granulocytes &gt; 1.0 \times 10^9/μL</td>
<td>IPA in 0/24 in AmB D vs 14/123 control</td>
<td>Mild nausea 0 discontinued</td>
<td>No systemic antifungal prophylaxis</td>
</tr>
<tr>
<td>Schwartz et al[2]</td>
<td>InAmB D n = 227, control n = 155</td>
<td>mean age (y): 46 InAmB D 48 control 6x NR</td>
<td>ALL, NHL, and solid tumors undergoing BMT</td>
<td>10 mg/5 mL over 15 min bid vs no inhalation</td>
<td>Neutrophils &gt; 1.0 \times 10^9/μL or stable neutrophils &gt; 0.5 \times 10^9/μL or &gt;day 50 Median 27 days</td>
<td>IA in 10/277 in AmB D vs 11/155 control</td>
<td>Cough, bad taste, and nausea 39 discontinued for ADRs</td>
<td>Oral AmB or fluconazole prophylaxis allowed</td>
</tr>
<tr>
<td>Nihlen et al[3]</td>
<td>InAmB D n = 354, historical control n = 257</td>
<td>median age (y): 47 InAmB D 44 control 53.8% men</td>
<td>Allogeneic SCT with GvHD receiving high-dose MP</td>
<td>25 mg/5 mL over 10-15 min daily vs no inhalation</td>
<td>2-3 months Mean 84 days</td>
<td>IPA in 9/354 in AmB D vs 17/257 control</td>
<td>Specific ADRs experienced NR but well tolerated 0 discontinued</td>
<td>No systemic antifungal prophylaxis Only 111 patients received in AmB D prophylaxis Albuterol pretreatment</td>
</tr>
<tr>
<td>Rijnders et al[4]</td>
<td>InLipAmB n = 139, control n = 132</td>
<td>mean age (y): 48 InLipAmB 50 control 58.3% men</td>
<td>Hematologic cancers undergoing chemo, allogeneic or auto logo us SCT</td>
<td>12.5 mg/2.5 mL over 30 min twice per wk</td>
<td>Neutrophils &gt; 0.3 \times 10^9/μL</td>
<td>IPA in 11/139 inLipAmB vs 23/132 placebo (P = .005)</td>
<td>Cough Discontinued for ≥ 1 wk 45% InLipAmB Vs 30% placebo</td>
<td>Oral fluconazole prophylaxis given 56 patients discontinued for delivery system limits (technical issues or being too weak)</td>
</tr>
<tr>
<td>Hullard-Pulstinger et al[5]</td>
<td>InLipAmB n = 93, historical control n = 105</td>
<td>mean age (y): 49 InLipAmB 49 control 65.2% men</td>
<td>AML and other acute leukemias and/or allogeneic SCT</td>
<td>12.5 mg over 10-20 min daily × 4 days then twice per wk vs no inhalation</td>
<td>Neutrophils &gt; 1.0 \times 10^9/μL</td>
<td>IA in 2.98 InLipAmB vs 4/118 control</td>
<td>Bad taste, cough, and nausea 41 discontinued</td>
<td>Majority received fluconazole prophylaxis 69% of patients received additional systemic antifungals</td>
</tr>
<tr>
<td>Chong et al[6]</td>
<td>InLipAmR n = 128, historical control n = 107</td>
<td>mean age (y): 55.6 InLipAmR 52.2 control 54.9% men</td>
<td>AML, MDS, and CML</td>
<td>12.5 mg/3 mL twice per wk vs no inhalation</td>
<td>Neutrophils &gt; 0.2 \times 10^9/μL \times 2 or &gt;0.5 \times 10^9/μL once</td>
<td>IPA in 12/126 inLipAmR vs 25/107 control (P = .0064)</td>
<td>ADRs and discontinuation rates NR Reported as well tolerated</td>
<td>Oral fluconazole prophylaxis given All analysis done on day 28</td>
</tr>
</tbody>
</table>

Abbreviations: ADR, adverse drug reaction; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ARR, absolute risk reduction; BMT, bone marrow transplant; CML, chronic myeloid leukemia; IA, invasive aspergillosis; IPA, invasive pulmonary aspergillosis (proven or probable); MDS, myelodysplastic syndrome; MP, methylprednisolone; NC, not conducted; NHL, non-Hodgkin lymphoma; NR, not reported; NS, not significant; RCT, randomized controlled trial; RRR, relative risk reduction; SCT, stem cell transplant; wk, week; y, years.
Inhaled AmB

- 40 allo BMT, non-comparative ABLC 1x/day x 5 days then 1x/week x 13 week (458), + fluconazole
  - 25 withdrawal (empirical therapy), 1 IFI
  - AE’s common -cough and 16/40 (40%) pts developed >20% decrease FEV1 at least once after administration of drug

- 271 neutropenic heme malignancy patients (407 episodes) randomized
  - 2x/week L-AmB vs. placebo
  - Decreased incidence of IFI
  - Cough more common L-AmB

Alexander et al. Transpl Infect Dis 2006
“Real life” outcomes

- 127 AML patients L-AmB during 1st, 2nd cycle (2008) vs. 108 historic controls (2005-'08)
  - L-AmB prophylaxis associated with decreased IPA, systemic antifungal therapies (53 vs 30%), cost savings
  - Timing of administration important (trial design)

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Incidence of proven/probable invasive pulmonary aspergillosis (IPA) according to treatment.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control group (n = 108)</th>
<th>L-AmB inhalation group (n = 127)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>28/108</td>
<td>15/127</td>
<td>0.0066</td>
</tr>
<tr>
<td>First chemotherapy</td>
<td>16/108</td>
<td>10/127</td>
<td>0.0994</td>
</tr>
<tr>
<td>Second chemotherapy</td>
<td>11/92</td>
<td>3/99</td>
<td>0.0246</td>
</tr>
<tr>
<td>Third chemotherapy</td>
<td>0/34</td>
<td>0/38</td>
<td>N/A</td>
</tr>
<tr>
<td>Allogeneic HSCT</td>
<td>1/28</td>
<td>2/46</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

L-AmB, liposomal amphotericin B; HSCT, haematopoietic stem cell transplantation; N/A, not applicable.

* All 235 patients were used for this analysis, including patients who underwent HSCT.
* Patients who had their first or second chemotherapy cycle combined with another chemotherapy cycle or HSCT and developed proven/probable IPA were counted in the initial chemotherapy group.
Retrospective: alloBMT + GVHD

- Retrospective 611 alloBMT (‘96-'05) – inh AmB + fluconazole
  - Drugs started with steroids
  - Lower incidence IFI
  - Many clinical changes during this period
    - Conditioning, diagnosis (GM EIA)

Nihtinen et al. Transpl Infect Dis (2011)
Unmet Needs: Expanding list of agents that azoles complicate

- People with acute lymphocytic leukemia (ALL) receiving:
  - Vincristine-based remission-induction chemotherapy
- People with acute myelogenous leukemia (AML) receiving:
  - FLT-3 inhibitors (midostaurin)
  - BCL-2 inhibitors (venetoclax)
  - IDH1 or IDH2 inhibitors (ivosidenib or enasidenib)
- People with chronic lymphocytic leukemia (CLL), receiving targeted B cell therapies: ibrutinib, idelalisib, venetoclax
- People receiving any of these drugs for multiple types of disorders:
  - Ibrutinib (with other drugs) for CLL, Waldenstroms macroglobulinemia, lymphoma, or severe chronic graft vs. host disease, or relapsed/refractory lymphoma
Adjunctive Therapy

- Reports of successful therapy in concurrent tracheobronchial disease, structural lung disease.
- Multiple therapies (nAmB, voriconazole)
- Example case of fistula, empyema after tumor resection
- Complicated courses of concurrent therapies with severe influenza

Hanada et al. AJRCCM (2014)
Boots et al. Thorax 1999
Influenza – Associated Aspergillosis

- Increased recognition
- IAPA case definition distinct from tracheobronchitis
- Geographic and seasonal variation (strain)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Venue</th>
<th>Patients (n)</th>
<th>Aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin-Löeches et al</td>
<td>148 Spanish ICU 2009 - 2015</td>
<td>2901</td>
<td>IAA in 35 (1.2% of cohort and 7.2% of co-infections)</td>
</tr>
<tr>
<td>Rodriguez-Goncer et al</td>
<td>Single UK tertiary center 2012 - 2016</td>
<td>134</td>
<td>IPA in 10 (7%), IAA in 5 (3.5%)</td>
</tr>
<tr>
<td>Cavayas et al</td>
<td>ECMO international registry (&gt;300 centers), 2006 - 2016</td>
<td>19,697</td>
<td>Aspergillus colonization and/or infection in 272 (1.4%)</td>
</tr>
<tr>
<td>Contou et al</td>
<td>Single center Chinese ICU with H1N1 influenza, 2017 - 2018</td>
<td>19</td>
<td>IFI in 11 (57.9%); IPA in 5 (26.3%)</td>
</tr>
<tr>
<td>Rogge et al</td>
<td>Influenza patients in ICUs in 8 centers in Netherlands, 2015-2016</td>
<td>144</td>
<td>IAA in 23 (16%)</td>
</tr>
<tr>
<td>Beumer et al</td>
<td>Influenza patients admitted to 2 hospitals in Netherlands, 2015-2016</td>
<td>200</td>
<td>IFI in 15/199 (7.5%)</td>
</tr>
<tr>
<td>Ku et al</td>
<td>Influenza patients admitted to one hospital in Taiwan, 2015 – 2016</td>
<td>124</td>
<td>IAA in 38/124 (31%)</td>
</tr>
<tr>
<td>Schauwvliegh et al</td>
<td>Influenza patients admitted to ICUs from 7 centers in Belgium and Netherlands, 2009 - 2016</td>
<td>432</td>
<td>IAA in 83 (19%)</td>
</tr>
<tr>
<td>Huang et al</td>
<td>Influenza patients admitted to ICU in one center in China, 2017 - 2018</td>
<td>64</td>
<td>IAA in 18 (28%)</td>
</tr>
<tr>
<td>Schwartz et al</td>
<td>Influenza patients in one Canadian center, 2014 – 2019</td>
<td>650</td>
<td>IAA in 8 / 111 (7.2%) ICU patients</td>
</tr>
<tr>
<td>Zou et al</td>
<td>Influenza (H7N9) patients admitted to 17 hospitals in China, 2013 – 2018</td>
<td>335</td>
<td>IAA in 18 (5.4%)</td>
</tr>
</tbody>
</table>
Influenza – Associated Aspergillosis

- French retrospective study 2010-19
  - 45/213 (21%) with IPA
  - 10 (29%) with tracheobronchitis (ITBA)
  - Sporulating in airway, invasive disease
  - Higher fungal markers
  - Worse survival

Nyga et al. AJRCCM 2020
COVID-Associated Pulmonary Aspergillosis

China | Anecdotal autopsy reports with early concerns for *Aspergillus* infection

France | CAPA in 9/27 (33%) patients in different ICUs

Belgium | Case series of 7/20 (34%) ventilated patients at two hospitals, some pathology-proven

Italy | Prospective, study reports CAPA in 30/108 (27.7%) ventilated patients

Netherlands | Pathology review in 6 CAPA patients

China | CAPA in 7%, of 104 COVID-19 patients in one hospital

Pakistan | CAPA in 5/23 (21.7%) ventilated patients in 1 hospital

Spain | Series of 10 putative or probable CAPA cases

Denmark | 2/8 ECMO patients with CAPA

U.K. | 19/135 (14%) CAPA in multiple ICUs

U.S & Spain | 20 cases from 2 centers

Jan - Feb | Mar - Apr | May - June | July - Sep
Conclusions

• Inhaled antifungals compelling for prevention of IFI
  – Proof shown in heme – neutropenia
  – Potential utility in severe viral infections

• Therapeutic efficacy suggested, particularly with airway complications
Thank you

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